REMARKS

Applicants have amended the specification to delete the claim of priority to US Application 09/380137 filed 8/25/1999, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/088030 filed 6/4/1998.

Applicants have cancelled Claims 14-17 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claims 6 and 9 to recite "selected from the group consisting of amino acids 34 to 56, 81 to 109, 127 to 214, 232 to 253 and 275 to 321 of SEQ ID NO: 10." Support for this amendment can be found throughout the specification as filed, for example, at Figure 10 and paragraphs [0011] and [0017].

Applicants thank the Examiner for his review of the instant application. Claims 6-7, 9, and 11-13 are presented for examination. Applicants respond below to the specific rejections raised by the Examiner in the pending Office Action. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

In the response mailed December 7, 2004, Applicants requested that inventors Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, and Colin K. Watanabe be deleted from the instant application, as these inventors' inventions were no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) was paid.

In the next Office Action, mailed March 30, 2005, the Examiner acknowledged the chance in inventorship, and stated that the application would be forwarded to the OIPE for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Applicants note that the information on the PTO's website still lists the original inventors. Applicants request that the Examiner again forward the application to the OIPE to have the inventorship information changed to reflect the deletion of Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, and Colin K. Watanabe from the instant application.

Rejection Under 35 U.S.C. §101 – Utility

The Examiner maintains his rejection of the pending claims under 35 U.S.C. § 101 as lacking a specific and substantial asserted utility or a well established utility for the reasons of record.

For the reasons set forth below, Applicants respectfully disagree. Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants address each of the Examiner's arguments in turn as presented in the pending Office Action.

The PTO has Concluded that the data in Example 18 are Sufficient to Establish the Utility of the Claimed Invention

As an initial matter, Applicants point out that in other applications filed by Applicants that rely on *data from the exact same disclosure, Example 18*, and in which the Applicants have submitted *substantially the same references* in support of their asserted utility, the PTO has concluded that:

> Based on the totality of evidence of record, **one of skill in the art would find it more likely than not that an increase in message as measured by RTPCR would be predictive of an increase in protein expression levels,** absent evidence to the contrary. Therefore, the data presented in Example 18, which demonstrates differential expression of nucleic acids encoding PRO1180, also supports a conclusion of differential expression of PRO1180 polypeptide. Therefore, one of ordinary skill in the art would be able to use the PRO1180 polypeptide diagnostically for distinguishing normal kidney and rectal tumor tissues compared to kidney tumor and normal rectal tissue, as asserted by Applicant. *Examiner's Reasons for Allowance, Application No. 10/063,529* (emphasis added).

See also *Examiners Reasons for Allowance* in Application No. 10/063,530, No. 10/063,524, No. 10/063,582, and No. 10/063,583, all of which conclude that the data presented in Example 18, which demonstrate differential expression of the nucleic acids encoding certain PRO polypeptides, also support a conclusion of differential expression of the PRO polypeptides,

making the claimed PRO polypeptides and antibodies that bind the PRO polypeptides useful for diagnostic purposes.

Applicants therefore request that the Examiner recognize the utility of the claimed invention, supported by the data presented in Example 18 and the numerous cited references, as was done in the other applications referenced above. The Patent Office's conclusion that "one of skill in the art would find it more likely than not that an increase in message as measured by RTPCR would be predictive of an increase in protein expression levels," is not dependent on the particular molecule being claimed, but instead represents a conclusion regarding the state of the art based on the record. Therefore, it does not suffice to say that each case must be decided on its own merits based on the evidence of record without offering an explanation of how the record is materially different such that a different outcome is warranted.

Duty of the Examiner in Examination of an Application

Applicants respectfully remind the Examiner that he has a duty to consider and respond to Applicants' arguments in an attempt to clarify the issues in dispute:

> The examiner should never lose sight of the fact that in every case the applicant is entitled to a full and fair hearing, and that a clear issue between applicant and examiner should be developed, if possible, before appeal. *M.P.E.P. §706.07* (emphasis added).

Applicants have attempted to respond to each of the Examiner's previous arguments, pointing out what the Applicants view as the factual errors or flaws in the Examiner's reasoning. Applicants respectfully request that the Examiner respond to Applicants' arguments in an attempt to clarify the issues in dispute prior to appeal.

Hu et al. and LaBaer References

In response to Applicants arguments that Hu's and LaBaer's statements regarding microarray data are not relevant to the pooled sample RT-PCR data of the instant application, the Examiner states:

> Applicants' arguments have been fully considered but they are not persuasive. From the evidence provided it cannot be ascertained if Kuo's micro array data was [*sic*] consistent or inconsistent with Kuo's RT-PCR data. Therefore, Applicants' reliance on Kuo is misplaced. *Office Action* at 3.

This response does not address Applicants' arguments regarding Hu and LaBaer. Presumably, by "the evidence provided," the Examiner is referring to Kuo. Applicants have not asserted that Kuo's microarray data is consistent or inconsistent with Kou's PCR data. Whether it is consistent or inconsistent is irrelevant to Applicants' argument, which is that those of skill in the art recognize that data generated by RT-PCR is more reliable, sensitive and accurate than microarray data. Kuo supports this assertion by stating in comparison to microarrays: "Use of more reliable and sensitive analyses, such as reverse transcriptase polymerase chain reaction...." One does not need to know if Kuo's RT-PCR data was consistent with Kuo's microarray data to rely on this statement any more than one needs to know what data LaBaer is relying on for the statement quoted by the Examiner – the Examiner cannot rely on the unsupported opinion of LaBaer, and then reject Kuo's statement because it allegedly lacks support.

Kuo is not cited to provide a basis for doubting Hu and LaBaer's statements. While Applicants do question the truth of Hu and LaBaer's unsupported opinions, the accuracy of their statements is of no relevance because they are discussing microarray data, not pooled sample RT-PCR data as in the instant application. Therefore, Hu and LaBaer's statements cannot support a rejection of Applicants' pooled sample RT-PCR data.

The Examiner must explain how opinions regarding microarray data, even if true, are applicable to pooled sample RT-PCR data, given Applicants' assertions and supporting evidence that one of skill in the art would recognize RT-PCR as more reliable, sensitive and accurate. Until the Examiner provides evidence that transcript changes detected by PCR analysis of pooled normal and tumor samples are often "attributable to disease-independent differences between the samples," the Examiner's rejection of the data in Example 18 based on Hu and LaBaer is unsupported and without merit.

First Grimaldi Declaration

With respect to Applicants' arguments that Hu and LaBaer are silent regarding the reliability of pooled samples, which are incorporated herein by reference, the Examiner states:

> Applicants' arguments have been fully considered but they are not persuasive. The utility of the PRO874 polypeptide lies in its ability to differentiate normal tissue from tumor tissue. The first Grimaldi declaration states that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. This statement is in contrast to the specification's teachings, which discloses:

> Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. Page 140, paragraph 0350.
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> ... In practicing the invention some value for PRO874 polypeptide expression must be obtained in order to distinguish normal tissue from tumor tissue. Establishing a cutoff value for this distinction would be difficult unless one knows the typical degree of variation within the pool, which Applicants have not provided. ... Without knowledge of the typical degree of variation within the pool one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue. Pooled samples would also obscure the variation between samples, making the disclosed results for PRO874 polynucleotide expression less useful, accurate and informative than if results from individual samples had been provided. In fact the range of values from normal and/or tumor tissue could be so broad that it would be impossible to distinguish normal tissue from tumor tissue. Hu and LaBaer are evidence that a skilled artisan would consider the precise level of PRO874 gene expression as relevant. *Office Action* at 3-4 (emphasis added).

The Examiner presents no evidence to support these assertions. Thus, the Examiner uses conclusory and unsupported arguments as the basis for dismissing the declaration of an expert. As such, the Examiner's position is inconsistent with the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered" (*66 Fed. Reg. 1098, Part IIB (2001)*) and also is inconsistent with the requirement that the Examiner support his assertions of fact. *See In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001). Absent supporting evidence, it is inappropriate for the Examiner to dismiss Applicants' arguments and Mr. Grimaldi's opinion regarding pooled samples simply because the Examiner wishes to take a contrarian position on the use of pooled samples in diagnostics.

Regarding the substance of the above-quoted text from the Examiner regarding pooled samples, Applicants traverse this position and maintain that their expert has established that "[d]ata from pooled samples is more likely to be accurate than data obtained from a sample from a single individual." *First Grimaldi Declaration* at ¶5. As to the Examiner's statement that "[i]n fact the range of values from normal and/or tumor tissue could be so broad that it would be

impossible to distinguish normal tissue from tumor tissue," (*Office Action* at 4, emphasis added), Applicants note that the Grimaldi declaration make clear that, in fact, "the results of the gene expression studies indicate that the genes of interest can be used to differentiate tumor from normal." *First Grimaldi Declaration* at ¶7. Applicants refrain from further rebutting the Examiner 's assertions because there presently are no facts on the record to support a position other than that of Mr. Grimaldi's. It is incumbent upon the Examiner to provide evidentiary support for the assertions regarding pooled samples so that Applicants can address this issue on appeal. *See In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001).

As for the Examiner's statement that the first Grimaldi declaration is "in contrast with the specification's teachings," (see *Office Action* at 3), Applicants do not know how to respond since the Examiner has not explained how the declaration is in contrast with the quoted portion of the specification or what relevance any contrast between the two statements has to Applicants' asserted utility. The specification states: "Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject." *Specification* at ¶[0530] (emphasis added). Applicants fail to see how this is in contrast to statements that pooled tumor tissue and pooled corresponding normal tissue were used. It is incumbent upon the Examiner to explain how these statements are "in contrast" and what the relevance of the "contrast" is to Applicants' asserted utility so that Applicants can address this issue on appeal.

Similarly, the Examiner's statement that "Hu and LaBaer are evidence that a skilled artisan would consider the precise level of PRO874 gene expression as relevant" is not supported by any reasoning or citation to Hu or LaBaer. Applicants' are unaware of any teaching in Hu regarding the need for a "precise level of PRO874 gene expression" to use it as a molecular marker to distinguish tumor tissue from normal tissue. In fact, Hu and LaBaer teach nothing at all regarding developing diagnostic markers of cancer. Second, Hu and LaBaer do not discuss the precise level of mRNA expression, but instead discuss relative differences such as 2-fold, 5-fold or 10-fold. *See Hu* at Abstract; LaBaer at 976. Rather than supporting the Examiner's arguments, Hu and LaBaer support Grimaldi's statement that "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." The Examiner must explain how Hu and LaBaer support his

assertion that the precise level of gene expression is required, rather than the relative difference between tumor and normal tissue as asserted by Grimaldi. Applicants request that the Examiner clarify his position to simplify the issues on appeal.

To the extent that the Examiner is attempting to argue that based on Hu and LaBaer one of skill in the art would consider the precise level of the relative difference (e.g. 2-fold, 5-fold, or 10-fold) important, Applicants have previously addressed why Hu and LaBaer's statements regarding 2-fold changes in microarray data are not relevant to Applicants' pooled RT-PCR data.

Applicants' Analogy to Gas Mileage

Applicants have offered several illustrations to demonstrate why references such as Haynes *et al.* and Gygi *et al.* that rely on a global ratio common between all steady state mRNA levels and all steady state protein levels are not relevant to Applicants' assertions regarding changes in mRNA level for a particular gene leading to changes in the level of the encoded protein. The Examiner responds by arguing:

> Applicants' arguments have been fully considered but they are not persuasive. Continuing with applicants' analogy, it is noted that applicants are not comparing the PRO874 polypeptide miles per gallon of PRO874 mRNA gas in a tissue sample with the PRO874 polypeptide miles per different amount of PRO874 mRNA gas in the same tissue sample. Applicants' are assuming a change in PRO874 polypeptide expression in two different cell samples without knowing the correlation between the change, if any, in PRO874 mRNA expression and the assumed change in PRO874 polypeptide expression. ... Just as one could not predict the distances traveled on a gallon of gas in two different cars without knowing the mpg in each car, one could not predict a change in protein expression in two different cell samples without knowing that the change in mRNA is associated with a corresponding change in the level of protein. Maybe if you added two gallons of PRO874 mRNA gas to the tumor cell you might travel twice as many PRO874 polypeptide miles as compared to one gallon of PRO874 mRNA gas in the normal cell, all else being equal. However, the PRO874 polypeptide miles per gallon of PRO874 mRNA gas in either the tumor cells or the normal cells is unknown. According to the first and second Polakis declarations, your PRO polypeptide miles per gallon of gallon of PRO mRNA gas may vary in tumor cells and normal cells. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the first and second Polakis declarations. In the absence of any specific data regarding PRO874 polypeptide expression, the fact that there

> may be a commonly understood general rule or dogma is insubstantial evidence of the diagnostic utility of the PRO874 polypeptide. Applicants have not provided any testing of PRO874 polypeptide expression. Applicants do not disclose the PRO874 polypeptide miles traveled per gallon of PRO874 mRNA gas in either the tumor cells or the normal cells. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO874 polypeptide will exhibit the asserted diagnostic behavior. *Office Action* at 4-5 (emphasis added).

These arguments do not address Applicants' assertion that references like Haynes and Gygi are irrelevant because they rely on the premise that there a global ratio common between all steady state mRNA levels and all steady state protein levels. Whether such a ratio exists does not matter to Applicants' assertions regarding changes in mRNA leading to changes in protein level. None of the Examiner's arguments are directed to the distinction between references like Haynes and Gygi, and the references cited by Applicants to support Applicants' assertions regarding differential mRNA expression. Instead, the Examiner's arguments attack Applicants' assertions that a general correlation between changes in mRNA and protein exist, and that one of skill in the art would rely on such correlation. These arguments do not address Applicants' arguments that Haynes and Gygi are irrelevant.

Applicants invite the Examiner to either acknowledge that references like Haynes and Gygi which are premised on a global ratio of mRNA to protein are irrelevant, including their conclusions that direct measurement of protein levels is required, and withdraw his reliance on these references, or explain how such references are relevant to Applicants' assertions regarding differential mRNA expression leading to differential protein expression. Doing so would clarify the issues in dispute for appeal.

Applicants' have previously responded to the substance of Examiner's arguments articulated above. Essentially, the Examiner's entire argument can be summarized thus:

> The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the first and second Polakis declarations. In the absence of any specific data regarding PRO874 polypeptide expression, the fact that there may be a commonly understood general rule or dogma is insubstantial evidence of the diagnostic utility of the PRO874 polypeptide. *Office Action* at 5 (emphasis added).

Applicants have presented overwhelming evidence that changes in mRNA generally lead to changes in the corresponding level of the encoded protein, including the declarations of three experts in the field, and over 100 references which directly or indirectly support this position.

Were the Examiner to acknowledge that based on the record, Applicants have established that there is such a general rule or correlation, rather than stating that there "may be", the remaining issue regarding the Examiner's argument above would be whether the Applicants can rely on a general rule with admitted exceptions to provide utility, or if Applicants must provide specific evidence of the PRO874 polypeptide expression. The Examiner apparently believes that if there is any exception to a correlation relied on for utility, a doubt is raised regarding the utility since it is not known if the claimed molecule follows the rule or the exception, and therefore specific direct evidence of utility is required. Applicants assert that a correct reading of the utility standard articulated by the Courts and the PTO indicate that the correlation need to be absolute or exact, but only reasonably indicative of the asserted utility. *See Nelson v. Bowler*, 626 F.2d 853, 856-57; *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051; *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564. Applicants could then appeal this issue to the Board of Patent Appeals and Interferences for clarification.

Therefore, in an attempt to clarify the issues in dispute, Applicants request that the Examiner acknowledge that based on a careful consideration of the ***entire record***, Applicants have established by a preponderance of the evidence (*i.e.* more likely than not) that those of skill in the art recognize that changes in mRNA level for a particular gene generally, but not always, lead to a change in the level of the encoded protein. Doing so would simplify issues for appeal.

Allman et al. Reference

Applicants have argued that the Allman et al. reference is not contrary to Applicants' assertion that, generally, a change in mRNA expression levels leads to a change in the encoded protein expression level. The Examiner has responded by arguing:

> Applicant's arguments have been fully considered but they are not persuasive. If one is to argue, as Appellants have argued, that because PRO874 transcripts are differentially expressed in tumors it is more likely than not that the PRO874 polypeptide is similarly differentially expressed in tumors, and therefore the PRO874 polypeptide and antibodies can be used for tumor diagnosis, then one must also accept the argument that because resting B cells and germinal center B

> cells express similar BCL-6 mRNA levels it is more likely than not that the BCL-6 protein is not differentially expressed in these two cell populations, and therefore the BCL-6 protein and antibodies thereto cannot be used as a marker for germinal center B cells. One must also accept the argument that because germinal center B-cells express dramatically more BCL-6 protein than resting B cells it is more likely than not that BCL-6 mRNA is differentially expressed in these two cell populations, and therefore BCL-6 mRNA can be used as a marker for germinal center B-cells. Allman indicates that this is not so and therefore Allman does not support Appellants' position. *Examiner's Answer Brief* at 22, incorporated by reference by Examiner in pending *Office Action* at 2 (emphasis added).

Applicants are not arguing that a change in polypeptide levels generally causes changes in mRNA levels or that polypeptide levels serve as indicators of mRNA levels. To argue so would conflate cause and effect. Nor do Applicants argue that a change in mRNA levels is the sole cause of changes in the level of the encoded polypeptide. Applicants merely submit that one skilled in the art would expect that a change in mRNA levels for a particular gene would generally lead to a corresponding change in levels of the encoded polypeptide. Allman is consistent with Applicants' contentions because Allman teaches that for cells expressing higher levels of BCL-6 mRNA, BCL-6 polypeptide levels also were higher, relative to BCL-6 polypeptide levels in cells that expressed lower levels of BCL-6 mRNA. Accordingly, Allman does not support a rejection of the claims for lacking utility.

It is not inconsistent for the Applicant to assert that changes in mRNA expression generally lead to changes in protein level, and at the same time acknowledge that not all changes in protein level are a result of changes in mRNA. Because not all changes in protein level are a result of changes in mRNA, one cannot assume that no change in BCL-6 mRNA ensures no change in BCL-6 protein, or that a change in BCL-6 protein is associated with a change in BCL-6 mRNA.

As an analogy, consider the assertion that increasing the number of home runs during a game increases a baseball team's score. It is not inconsistent to state that when no one is hitting home runs, you cannot assume that the team's score isn't increasing because there are other ways to increase the score (e.g. a bases loaded single). Similarly, it is not inconsistent to state that if a team's score increases, it does not necessarily mean that someone hit a home run. Scoring runs does not result in, or necessarily reflect, home run hitting, but home run hitting does cause scoring. Home run hitting is the cause, scoring is the effect. Similarly, increasing protein levels

does not cause, or necessarily reflect increased mRNA, but increased mRNA does generally cause increased protein. A change in mRNA level is the cause, a change in protein level is the effect. Applicants respectfully request that the Examiner acknowledge that his arguments based on Allman are conflating cause and effect, and that Allman is not contrary to Applicants' assertion that changes in mRNA level generally lead to corresponding changes in the encoded protein level. Doing so would simplify issues for appeal.

The Declarations of Dr. Polakis

Applicants have submitted a second declaration of Dr. Polakis, including data for evaluation by the Examiner. In response, the Examiner argues:

> The second Polakis declaration has been considered. Like the first Polakis declaration, the second Polakis declaration does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue.
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> The facts to be established are whether or not the disclosed change in PRO874 transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO874 transcripts and a corresponding change in PRO874 polypeptides levels. The declarations do not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue.
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> ... Both the first and second Polakis declarations indicate that the data was generated using microarray analysis, which applicants' have disparaged as inaccurate. ... Even if the examiner were to accept Dr. Polakis' conclusion, it still would be considered evidence that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer because 20% of the cases examined do not show a correlation, according to first Polakis declaration, and 10% of the cases examined do not show a correlation according to second Polakis declaration. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist. *Office Action* at 6-7 (emphasis added).

Applicants emphasize that they have not "disparaged as inaccurate" microarray data. Applicants have merely argued that conclusions regarding "disease-independent" differences between samples based on microarray data cannot be extended to RT-PCR data because those of

skill in the art recognize that the latter is more accurate, reliable, and sensitive than microarray data.

The Examiner continues to rely on his personal opinion that because there are exceptions to the general correlation, one of skill in the art would not rely on differential PRO874 mRNA expression data to predict PRO874 protein expression. The Polakis, Grimaldi, and Scott Declarations, all by experts in the field, state that the correlation is sufficiently reasonable that one of skill in the art would rely on differential mRNA expression data to predict protein expression.

Applicants offer the Scott, Grimaldi, and Polakis Declarations, not to unequivocally prove that PRO874 polypeptide is differentially expressed, but rather to prove that one of skill in the art would be more likely than not to believe that because the PRO874 mRNA as measured by RT-PCR is differentially expressed, the PRO874 polypeptide will likewise be differentially expressed. Applicants do not need to provide direct evidence of PRO874 polypeptide expression to establish the asserted utility. Indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101. *Nelson v. Bowler*, 626 F.2d 853, 856-57, *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051; *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564. In light of the proper utility standard, it is improper for the Examiner to reject the Polakis Declaration because it does not provide direct evidence of differential PRO874 polypeptide expression – that is not what the Polakis Declaration is required to do. Instead, the Polakis Declaration is evidence that Applicants' evidence of utility is sufficient to convince one of skill in the art that the asserted utility is more likely than not true.

Applicants request that the Examiner acknowledge that there are cases where direct evidence of utility is not required because there is a reasonable correlation between the asserted utility and the evidence provided. In such cases, declarations establishing the reasonableness of the correlation between the asserted utility and the evidence provided, as well as reliance thereon, are probative. While the Examiner may not agree that this is one of those cases, such an acknowledgement would place the Polakis Declaration in the proper perspective – evidence that one of skill in the art would rely on differential mRNA data to predict protein expression – rather than viewing it as insufficient because it does not contain direct evidence of PRO874 polypeptide expression.

The Examiner's Position is Inconsistent with the Utility Guidelines and the Courts

In response to Applicants' evidence and arguments, the Examiner takes the position that Applicants must present specific evidence directly demonstrating the utility of the claimed antibodies – specifically, direct evidence of differential expression of PRO874 polypeptide in tumor and normal tissue:

> Applicants' additional supporting references have also been considered. However, none of this evidence discloses anything specific regarding PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in nonnal tissue and tumor tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the first and second Polakis declarations.
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> ... Applicants have not provided any testing of PRO874 polypeptide expression. The specification does not establish if the disclosed change in PRO874 mRNA expression is one of those cases where this is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO874 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO874 polypeptide, the specification does not provide some immediate benefit to the public for the PRO874 polypeptide.
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> Applicant should provide substantial evidence of a diagnostic utility unless one of skill in art would accept such utility as obviously correct. There is no indication that a skilled artisan would accept without question that the reported change in PRO874 transcripts is tumor-dependent or that the PRO874 polypeptide is differentially expressed in tumor tissue as compared to normal tissue in a manner consistent with the reported change in PRO874 transcripts. Neither the specification nor any of Applicants' arguments, exhibits, declarations or other evidence provide any specific data disclosing if or how PRO874 polypeptide expression changes in tumor tissue. ... Without any evidence of the expression of PRO874 in tumor tissue this argument is of no avail to Applicants. Applicants' arguments, exhibits and declarations only show that it is not implausible that invention will work for its intended purpose. In view of the countervailing evidence, Applicants' arguments, exhibits and declarations are insufficient to

> meet the utility requirement because they are insubstantial evidence that expression of the PRO874 polypeptide changes in a manner that corresponds to the reported change in PRO874 transcripts. *Office Action* at 9-11 (emphasis added).

Thus, the PTO implies the following argument: (1) the evidence of record demonstrates that there are exceptions to the general rule that increased mRNA levels correspond to increased levels of the encoded polypeptide; (2) because such exceptions exist, it is mandatory that specific data of differential PRO874 polypeptide expression in esophageal tumor tissue as compared to normal esophageal tissue be disclosed; and (3) since such is not disclosed, the claimed polypeptides have no substantial utility.

Adopting the Examiner's standard for utility would result in a per se rule that a difference in mRNA expression cannot establish a utility for the encoded polypeptide and antibodies thereto. Thus, the Examiner chooses to heighten the utility requirement to require specific, direct evidence of utility when there are exceptions to a generally accepted rule that is relied upon for utility. This heightened utility requirement is inconsistent with the Utility Guidelines and the courts. There is no requirement that utility be dispositively proven:

> Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965) ... Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* 2107.02 VII (emphasis in original).

Nor is there requirement that only direct evidence of utility is sufficient to establish utility. Instead, it is established that indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101. *Nelson v. Bowler*, 626 F.2d 853, 856. Furthermore, there is no requirement that indirect evidence necessarily and always prove actual utility. Instead, there only need be a reasonable correlation between the indirect evidence and the asserted utility. *Id.* at 857, *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051. The indirect evidence need not absolutely prove the asserted utility. All that is required is that the tests be reasonably indicative of the asserted utility. In other words, there need only be a sufficient correlation between the indirect evidence and the utility so as to convince those skilled in the art, to a

reasonable probability, that the novel compound will possess the asserted utility. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564.

The Examiner appears to consider the above guidance from the courts inapplicable to the present situation because in those cases the claimed compound had been tested, and, in the present test, the claimed polypeptides have not been tested. However, the Examiner's position fails to recognize the issue in question for the above cases. The issue in question was whether or not Appellants' evidence (*in vitro* or animal testing of compound), which was different in nature from the asserted utility (therapeutic use of compound), was sufficient to fulfill the requirements of 35 U.S.C. §101 when there was a reasonable link between Appellants' evidence and the asserted utility. In the present case, Applicants submit that their evidence (differential mRNA expression) is reasonably linked to the asserted utility (diagnostic use of the encoded polypeptide). Insofar as it is uncontested that differential mRNA expression is reasonably linked to differential polypeptide expression, Applicants submit that such linkage is sufficient to fulfill the requirements of 35 U.S.C. §101 as provided by the guidance of the Utility Guidelines and the courts.

Finally, Applicants note that contrary to the Examiner's assertion that "[t]here is no indication that a skilled artisan would accept without question that ... the PRO874 polypeptide is differentially expressed in tumor tissue as compared to normal tissue in a manner consistent with the reported change in PRO874 transcripts," Applicants have provided the declarations of three experts in the field, and over 100 supporting references. This evidence establishes that one of skill in the art would be reasonably convinced that the PRO874 polypeptide will exhibit the asserted diagnostic utility, and case law establishes that this is sufficient. Thus, the Examiner's position is untenable in light of the evidence of record and relevant case law – exceptions to the correlation relied on for utility does not result in a requirement for direct evidence of the asserted utility.

Applicants' respectfully request that the Examiner reexamine his contention that only direct evidence of PRO874 polypeptide expression can provide the required evidence of utility:

> Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965) ... Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* 2107.02 VII (emphasis in original).

The Declaration of Dr. Scott

To support their assertion that a change in mRNA level generally leads to a corresponding change in the encoded protein level, Applicants previously submitted the declaration of Dr. Randy Scott. The Examiner responds by arguing:

> Applicants' arguments have been fully considered but they are not persuasive. The declaration under 37 CFR 1.132 filed by Randy Scott is insufficient to overcome the rejection of claims 6-7, 9 and 11-17 for lack of utility. Dr. Scott bases his conclusions on microarray data, which applicants have disparaged as inaccurate. Further, Dr. Scott does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in any type of tissue sample. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, ... Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO874 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO874 polypeptide, the specification does not provide some immediate benefit to the public for the PRO874 polypeptide. *Office Action* at 11-12 (emphasis added).

Applicants emphasize again that they have not "disparaged as inaccurate" microarray data. Applicants have merely argued that conclusions regarding "disease-independent" differences between samples based on microarray data cannot be extended to RT-PCR data because those of skill in the art recognize that the latter is more accurate, reliable, and sensitive than microarray data.

As to the remainder of the Examiner's argument – that because there are exception to the relationship between changes in mRNA and changes in protein, Applicants must provide actual testing of PRO874 polypeptide – Applicants note that the Scott Declaration states exactly the opposite. Dr. Scott, an independent expert in the field of molecular diagnostics, states:

> [I]t has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified ... **without the need to directly measure individual protein expression levels**. *Scott Declaration* at ¶10 (emphasis added).

Dr. Scott's declaration directly contradicts the personal opinion of the Examiner, and the Examiner has not given any reason to reject the Scott Declaration, other than the inaccurate statement that Applicants have disparaged microarray data. Without basis, the Examiner is ignoring the declaration of an independent expert in the field who states that one of skill in the art would rely on a correlation between changes in mRNA to predict changes in protein, in spite of the exceptions to the general correlation, without directly measuring the individual protein expression.

The Examiner has not explained his basis for rejecting Dr. Scott's opinion – he merely repeats the arguments made before the Scott Declaration was submitted. Applicants remind the Examiner that case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record **anew**. *See in re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976); *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). As the Examiner has previously stated, when considering the weight to be given an expert opinion, the Examiner should evaluate, among other things:

(1) The nature of the fact sought to be established.
(2) The strength of any opposing evidence.
(3) The interest of the expert in the outcome of the case.
(4) The presence or absence of factual support for the expert's opinion.

(1) The nature of the fact sought to be established: The nature of the fact to be established is whether one of skill in the art would believe that differential mRNA levels reflect differential protein levels, such that they would rely on this general correlation to predict changes in protein by measuring changes in mRNA without directly measuring the individual protein expression. The nature of this question is such that it is best answered by those who are actually practicing scientists in the field of molecular and cancer biology, like Dr. Scott.

(2) The strength of any opposing evidence: The Examiner has not submitted any opposing evidence. The Examiner continues merely to rely on a few references which he asserts establish that there are exceptions to the general correlation between changes in mRNA and changes in protein. Although Applicants dispute the relevance of the Examiner's evidence, they have acknowledged that exceptions exist. However, the fact sought to be established is not whether exceptions to the rule exist, but rather, whether the correlation between Applicants' evidence of utility and the asserted utility is well-established enough that one of skill in the art would accept Applicants' asserted utility based on the PRO874 RT-PCR mRNA data. The

Examiner has not presented any evidence that those of skill in the art would not rely on differential RT-PCR mRNA data to predict protein expression for diagnostic utility.

(3) The interest of the expert in the outcome of the case: Dr. Scott is an independent expert in the field. He is not an employee of the Assignee, nor is he an inventor of the instant application.

(4) The presence or absence of factual support for the expert's opinion: Dr. Scott relies on his extensive experience in the field, as well as the fact that an entire industry has developed around technology to assess differential mRNA expression. As stated previously, there would be little reason to study changes in mRNA expression levels if those changes did not result in corresponding changes in the encoded protein levels. In addition, Dr. Scott's conclusions are supported by the declarations of two other experts in the field, and over 100 other supporting references which Applicants have submitted.

When the factors outlined above are considered as a whole, it is clear that the Scott Declaration cannot simply be summarily dismissed. Applicants respectfully request that the Examiner properly consider the Scott Declaration, and articulate a proper basis for rejecting Dr. Scott's independent expert opinion – merely repeating the Examiner's personal opinion that one of skill in the art would require actual testing of the molecule is not a sufficient basis to reject the opinion of an expert in the field to the contrary, especially given the other evidence of record (3 expert declarations and over 100 references) which support Dr. Scott's conclusions.

Conclusion

Applicants have established that it is more likely than not that one of skill in the art would believe that because the PRO874 mRNA is differentially expressed in lung tumors as compared to normal lung tissue, the PRO874 polypeptide will likewise be differentially expressed in lung tumors. Accordingly, when the evidence is applied to the proper standard for utility, it is clear that this differential expression of the PRO874 polypeptide establishes the claimed polypeptides useful as diagnostic tools for cancer, particularly lung cancer. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The Examiner maintains his rejection of the pending claims under 35 U.S.C. § 112, first paragraph. Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Thus, since the enablement rejection is based on the rejection of the claims as lacking utility, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

The Examiner also maintains that the enablement would not be commensurate in scope with pending Claims 14-17. *Office Action* at 13-15. While Applicants do not agree with the Examiner, in order to expedite allowance of the remaining claims, Applicants have canceled claims 14-17, rendering this issue moot.

Rejections under 35 U.S.C. § 112, first paragraph – Written Description

The Examiner has maintained its rejection of Claims 14-17 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. While Applicants do not agree with the Examiner, in order to expedite allowance of the remaining claims, Applicants have canceled Claims 14-17, rendering this rejection moot.

Rejections under 35 U.S.C. § 112, first paragraph – Written Description, New Matter

The Examiner has rejected pending Claims 6-7, 9 and 11-13 under 35 U.S.C. §112, first paragraph, as containing new matter. *Office Action* at 18-21. Specifically, the Examiner objects to claim limitations related to amino acids 34-321, and residues 81-109 and 232-253 of SEQ ID NO:10. Applicants have argued that the Examiner's previous arguments misstate the written description standard and ignore the clear teaching of the specification.

In response, the Examiner makes the following arguments relating to residue #34:

> Applicants' arguments have been fully considered but they are not persuasive. The species methionine residue #34 as the starting amino acid is not supported by the generic disclosure because there is no express, implicit, or inherent support for this species to the exclusion of all the other species. There is no evidence of record that the naturally occurring PRO874 polypeptide actually starts at methionine residue #34. Therefore, the specification does not convey with reasonable clarity that Appellants were in possession of the invention now claimed. The limitation introduces new concepts and violates the description

> requirement of the first paragraph of 35 U.S.C. 112. *Office Action* at 19-20 (emphasis added)

This argument is not persuasive, as it ignores a fundamental principle of the written description requirement – it is the subject matter that is claimed that must be adequately described. Applicants' claims do not recite "the naturally occurring PRO874 polypeptide," or "to the exclusion of all the other species." All that is required to satisfy the written description requirement is that "the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." *M.P.E.P.* §2163.02 (internal citations omitted, emphasis added). Nothing in the test for written description requires that the claimed invention needs to be described "to the exclusion of all others" – numerous embodiments can be described even though only one or more are claimed. The instant case is similar to a generic chemical structure with a variable "R" group that is defined in the specification. Where the genus of chemicals defined by the structure is small (e.g. 8), the fact that a genus is described does not prevent the applicant from claiming a particular species by selecting a particular "R" group. There is no requirement that the particular claimed species be described "to the exclusion of all others," as the description of the small genus and various "R" groups is sufficient.

In the instant application, there are eight methionine residues in SEQ ID NO:10. At a minimum, as the Examiner has acknowledged, there is generic written description support for the "genus" of proteins starting at any one of these methionine. This "genus" contains eight immediately identifiable species since SEQ ID NO:10 is disclosed, and one of skill in the art knows which residues are methionine. Given the "generic" description, combined with the specifics of SEQ ID NO:10, each of the eight species in the "genus" is adequately described. This is particularly true for the claimed species, since methionine #34 is the first methionine in SEQ ID NO:10. Applicants request that the Examiner explain why there must be "express, implicit, or inherent support for this species **to the exclusion of all other species**," as Applicants are not aware of any support for this test in the M.P.E.P. or the case law.

Claims 6, 9 and 12-17 are further rejected under 35 U.S.C. §112, first paragraph, as containing new matter. The Examiner asserts:

> Applicants' arguments have been fully considered but they are not persuasive. The specification describes an isolated PRO polypeptide having at least about a recited % "amino acid sequence identity to a PRO polypeptide having a full-

> length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein." Page 8, 0014. See also page the paragraph bridging pages 28-29. The specification also describes "an isolated PRO polypeptide which is ... transmembrane domain-deleted" (page 9, 0017). However, the specification does not specifically define the 81-109 and 232-253 fragments of SEQ ID NO: 10 as either intracellular domains or an extracellular domains. Figure 10 discloses four transmembrane domains. Thus, the extracellular domains depend on how the polypeptide is arranged in the membrane. However, the specification does not disclose how the polypeptide is arranged in the membrane. The disclosure at page 8, paragraph 0014 and at the paragraph bridging pages 28-29 coupled with figure 10 and the newly added claim limitations, **imply** that the 81-109 and 232-253 fragments of SEQ ID NO: 10 are extracellular domains. The only specific disclosure of a fragment of a PRO polypeptide is in the context of an extracellular domain with or without the signal peptide. The specification does not disclose a specific fragment or fragments of the PRO polypeptide that is/are the intracellular or the extracellular domain or domains. Thus, the specification does not support the claiming of the 81-109 and 232-253 fragments of SEQ ID NO: 10. Hence, the newly added limitations constitute new matter, which introduces new concepts and violates the description requirement of the first paragraph of 35 U.S.C. 112. *Office Action* at 21 (emphasis added).

The Examiner's characterization of Applicants' arguments and the teachings of the specification is incorrect. As Applicants have previously explained, paragraph [0011] of the specification teaches:

> Another aspect the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. *Specification at* ¶[0011] (emphasis added).

Paragraph [0017] of the specification provides:

> Another aspect the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture. *Specification at* ¶[0017] (emphasis added).

Thus, the specification specifically discloses transmembrane domains of PRO874 and specifically contemplated transmembrane domain-deleted PRO polypeptides. Applicants' amendments are directed to such transmembrane domain-deleted PRO polypeptides. Applicants agree that the specification states that extracellular domains of the disclosed PRO polypeptides are contemplated. However, this does not negate the fact that Applicants specifically contemplated transmembrane domain-deleted PRO polypeptides, which does not require that all PRO polypeptides be or comprise an extracellular domain.

The Examiner's subjective belief that the claims "imply" that the recited portions of SEQ ID NO:10 are extracellular domains is irrelevant. The only issue is whether the subject matter as claimed is adequately described in the specification. The claims do not recite anything regarding "extracellular domains." Instead, the claims recite specific portions of SEQ ID NO:10, and the recited portions are adequately described by the specification as discussed above. The Examiner's subjective belief regarding what is implied by the claims is of no consequence.

In order to simplify issues on appeal, Applicants request that the Examiner acknowledge that Applicants specifically contemplated transmembrane domain-deleted PRO polypeptides. Since the Examiner provides no reason to consider the above-quoted portions of the specification insufficient to support the claims, other than his subjective belief regarding what is implied by the claims, the Examiner fails to sustain his assertion that these claims contain new matter. Accordingly, this ground for rejection of the claims must be removed.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Feb. 9, 2007

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